

IN THE SPECIFICATION:

Please replace the paragraph beginning at page 3, line 14, with the following rewritten paragraph:

- In an additional aspect, the present invention provides methods of quantifying the amount of a plurality of germline constructs comprising preparing mRNA from the plurality of cells to form an mRNA mixture, and adding at least three RNase protection probes (RPPs) selected from the group consisting of the sequences depicted in Figure 3 or 4 (SEQ ID NOS:1-13). An RNase protection enzyme (RPE) is added to the mixture, such that mRNA that is not protected is digested, and the amount of each germline mRNA is quantified.–

Please replace the paragraph beginning at page 3, line 23, with the following rewritten paragraph:

- Figure 3 (SEQ ID NOS:1-6) depicts the sequences of some “long” RPPs of the invention.–

Please replace the paragraph beginning at page 3, line 24, with the following rewritten paragraph:

- Figure 4 (SEQ ID NOS:7-13) depicts the sequences of some “short” RPPs of the invention.–

Please replace the paragraph beginning at page 12, line 6, with the following rewritten paragraph:

- A preferred coiled-coil presentation structure is as follows:

MGCAALESEVSALESEVASLESEVAAL**GRGDMP**LA**AVKSKL**SAVKSKLASVKSKLA**ACGPP** (SEQ ID NO:14). The underlined regions represent a coiled-coil leucine zipper region defined previously (see Martin et al., EMBO J. 13(22):5303-5309 (1994), incorporated by reference). The bolded GRGDMP (SEQ ID NO:15) region represents the loop structure and when appropriately replaced with randomized peptides (i.e. candidate bioactive agents, generally depicted herein as (X)_n, where X is an amino acid residue and n is an integer of at least 5 or 6) can be of variable length. The replacement of the bolded region is facilitated by encoding restriction endonuclease sites in the underlined regions, which allows the direct incorporation of randomized oligonucleotides at these positions. For example, a preferred embodiment generates a XhoI site at the double underlined LE site and a HindIII site at the double-underlined KL site.–

Please replace the paragraph beginning at page 12, line 25, with the following rewritten paragraph:

- A preferred minibody presentation structure is as follows:

MGRNSQATSGFTF*SHFY*MEWVRGGEYIAASR**HKH***HNKY***TTEYSASVKGRYIVSRDTSQSILYLQ**
KKKGPP (SEQ ID NO:16). The bold, underline regions are the regions which may be randomized. The italicized phenylalanine must be invariant in the first randomizing region. The entire peptide is cloned in a three-oligonucleotide variation of the coiled-coil embodiment, thus allowing two different

randomizing regions to be incorporated simultaneously. This embodiment utilizes non-palindromic BstXI sites on the termini.—

Please replace the paragraph beginning at page 13, line 17, with the following rewritten paragraph:

— In a preferred embodiment, the targeting sequence is a nuclear localization signal (NLS). NLSes are generally short, positively charged (basic) domains that serve to direct the entire protein in which they occur to the cell's nucleus. Numerous NLS amino acid sequences have been reported including single basic NLSes such as that of the SV40 (monkey virus) large T Antigen (Pro Lys Lys Lys Arg Lys Val (SEQ ID NO:17)), Kalderon (1984), et al., Cell, 39:499-509; the human retinoic acid receptor- β nuclear localization signal (ARRRRP (SEQ ID NO:18)); NF κ B p50 (EEVQRKRQKL (SEQ ID NO:19); Ghosh et al., Cell 62:1019 (1990); NF κ B p65 (EEKRKRTYE (SEQ ID NO:20); Nolan et al., Cell 64:961 (1991); and others (see for example Bouliskas, J. Cell. Biochem. 55(1):32-58 (1994), hereby incorporated by reference) and double basic NLSes exemplified by that of the Xenopus (African clawed toad) protein, nucleoplasmin (Ala Val Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys Lys Leu Asp (SEQ ID NO:21)), Dingwall, et al., Cell, 30:449-458, 1982 and Dingwall, et al., J. Cell Biol., 107:641-849; 1988). Numerous localization studies have demonstrated that NLSes incorporated in synthetic peptides or grafted onto reporter proteins not normally targeted to the cell nucleus cause these peptides and reporter proteins to be concentrated in the nucleus. See, for example, Dingwall, and Laskey, Ann, Rev. Cell Biol., 2:367-390, 1986; Bonnerot, et al., Proc. Natl. Acad. Sci. USA, 84:6795-6799, 1987; Galileo, et al., Proc. Natl. Acad. Sci. USA, 87:458-462, 1990.—

Please replace the paragraph beginning at page 14, line 7, with the following rewritten paragraph:

— In a preferred embodiment, the fusion partner is a stability sequence to confer stability to the candidate bioactive agent or the nucleic acid encoding it. Thus, for example, peptides may be stabilized by the incorporation of glycines after the initiation methionine (MG or MGG0), for protection of the peptide to ubiquitination as per Varshavsky's N-End Rule, thus conferring long half-life in the cytoplasm. Similarly, two prolines at the C-terminus impart peptides that are largely resistant to carboxypeptidase action. The presence of two glycines prior to the prolines impart both flexibility and prevent structure initiating events in the di-proline to be propagated into the candidate peptide structure. Thus, preferred stability sequences are as follows: MG(X)_nGGPP (SEQ ID NO:22), where X is any amino acid and n is an integer of at least four.—

Please replace the paragraph beginning at page 15, line 14, with the following rewritten paragraph:

— In a preferred embodiment, the fusion partner includes a linker or tethering sequence, as generally described in PCT US 97/01019, that can allow the candidate agents to interact with potential targets unhindered. For example, when the candidate bioactive agent is a peptide, useful linkers include glycine-serine polymers (including, for example, (GS)_n, (GSGGS)_n (SEQ ID NO:23) and (GGGS)_n (SEQ ID NO:24), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers such as the tether for the shaker potassium channel, and a large variety of other flexible linkers, as will be appreciated by those in the art. Glycine-serine polymers are preferred since both of these amino acids are relatively unstructured, and therefore may be able to serve as a neutral tether between components. Secondly, serine is hydrophilic and therefore able to solubilize what could be a globular glycine chain. Third, similar chains have been shown to be effective in joining subunits of recombinant proteins such as single chain antibodies.—

Please replace the paragraph beginning at page 18, line 20, with the following rewritten paragraph:

— RPA probes include for example the germline Igα-2 probe depicted in Figure 3, sheet 1 (SEQ ID NO:1). This RPA probe comprises a nucleic acid sequence about 532 nucleotides in length. In a preferred embodiment, the present invention provides Igα-2 RPA probes consisting essentially of nucleotides from about 1 to about 530 of the Igα2 probe depicted in Figure 3. In another preferred embodiment, the present invention provides Igα2 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 530 or about 520 or about 510 or about 500 or about 490 or about 480 or about 470 or about 460 or about 450 or about 440 or about 430 of the Igα2 probe depicted in Figure 3.—

Please replace the paragraph beginning at page 18, line 28, with the following rewritten paragraph:

— Also provided by the present invention is the germline Igα-2 probe depicted in Figure 4, sheet 1 (SEQ ID NO:8). This RPA probe comprises a nucleic acid sequence about 430 nucleotides in length. The Igα-2 probe sequence depicted in Figure 4 is preferred over the Igα-2 probe sequence depicted in Figure 3 (SEQ ID NO:1). In a preferred embodiment, the present invention provides Igα-2 RPA probes consisting essentially of nucleotides from about 1 to about 430 of the Igα2 probe depicted in Figure 4. In another preferred embodiment, the present invention provides Igα2 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 430 or about 425 or about 420 or about 415 of the Igα2 probe depicted in Figure 4.—

Please replace the paragraph beginning at page 19, line 2, with the following rewritten paragraph:

- Also provided herein are Ig α -2 RPA probes comprising nucleic acid sequences longer than that depicted in Figure 3 (SEQ ID NO:1), which comprise the Ig α -2 nucleic acid sequence depicted in Figure 3 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig α -2 probes are designed as complements of fragments of the nucleic acid sequence conceptually generated by fusion of the nucleic acid sequences depicted at Genbank accession numbers L04541 (being 5') and AL389978 (being 3'). The 3' nucleotides (up to about 15 nucleotides) of Ig α -2 RPA probes which are in addition to the Ig α 2 probe sequence depicted in Figure 3 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of L04541 and AL389978 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 19, line 11, with the following rewritten paragraph:

- RPA probes include for example the germline Ig-epsilon probe depicted in Figure 3, sheet 1 (SEQ ID NO:2). This RPA probe comprises a nucleic acid sequence about 202 nucleotides in length. In a preferred embodiment, the present invention provides Ig-epsilon RPA probes consisting essentially of nucleotides from about 1 to about 200 of the Ig-epsilon probe depicted in Figure 3. In another preferred embodiment, the present invention provides Ig-epsilon RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 200 or about 195 or about 190 or about 185 of the Ig-epsilon probe depicted in Figure 3.—

Please replace the paragraph beginning at page 19, line 18, with the following rewritten paragraph:

- Also provided by the present invention is the germline Ig-epsilon probe depicted in Figure 4, sheet 1 (SEQ ID NO:9). This RPA probe comprises a nucleic acid sequence about 202 nucleotides in length. In a preferred embodiment, the present invention provides Ig-epsilon RPA probes consisting essentially of nucleotides from about 1 to about 200 of the Ig-epsilon probe depicted in Figure 4. In another preferred embodiment, the present invention provides Ig-epsilon RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 200 or about 195 or about 190 or about 185 of the Ig-epsilon probe depicted in Figure 4.—

Please replace the paragraph beginning at page 19, line 25, with the following rewritten paragraph:

- Also provided herein are Ig-epsilon RPA probes comprising nucleic acid sequences longer than that depicted in Figure 3 (SEQ ID NO:2), which comprise the Ig-epsilon nucleic acid sequence depicted in Figure 3 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig-epsilon probes are designed as complements of fragments of the nucleic acid sequence

conceptually generated by fusion of the nucleic acid sequences depicted at Genbank accession numbers X56797 (being 5') and J00222 (being 3'). The 3' nucleotides (up to about 15 nucleotides) of Ig-epsilon RPA probes which are in addition to the Ig-epsilon probe sequence depicted in Figure 3 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of X56797 and J00222 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 20, line 1, with the following rewritten paragraph:

— RPA probes include for example the germline Ig gamma-1 probe depicted in Figure 3, sheet 1 (SEQ ID NO:3). This RPA probe comprises a nucleic acid sequence about 593 nucleotides in length. In a preferred embodiment, the present invention provides Ig gamma-1 RPA probes consisting essentially of nucleotides from about 1 to about 590 of the Ig gamma-1 probe depicted in Figure 3. In another preferred embodiment, the present invention provides Ig gamma-1 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 590 or about 580 or about 570 or about 560 or about 550 or about 540 or about 530 or about 520 or about 510 or about 500 or about 490 or about 480 or about 470 or about 460 or about 450 or about 440 or about 430 or about 420 or about 410 or about 400 or about 390 or about 380 or about 370 of the Ig gamma-1 probe depicted in Figure 3.—

Please replace the paragraph beginning at page 20, line 11, with the following rewritten paragraph:

— Also provided by the present invention is the germline Ig gamma-1 probe depicted in Figure 4, sheet 2 (SEQ ID NO:10). This RPA probe comprises a nucleic acid sequence about 370 nucleotides in length. The Ig gamma-1 probe sequence depicted in Figure 4 is preferred over the Ig gamma-1 probe sequence depicted in Figure 3 (SEQ ID NO:3). In a preferred embodiment, the present invention provides Ig gamma-1 RPA probes consisting essentially of nucleotides from about 1 to about 370 of the Ig gamma-1 probe depicted in Figure 4. In another preferred embodiment, the present invention provides Ig gamma-1 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 370 or about 365 or about 360 or about 355 of the Ig gamma-1 probe depicted in Figure 4.—

Please replace the paragraph beginning at page 20, line 19, with the following rewritten paragraph:

— Also provided herein are Ig gamma-1 RPA probes comprising nucleic acid sequences longer than that depicted in Figure 3 (SEQ ID NO:3), which comprise the Ig gamma-1 nucleic acid sequence depicted in Figure 3 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig gamma-1 probes are designed as complements of fragments of the nucleic acid sequence conceptually generated by fusion of the nucleic acid sequences depicted at Genbank

accession numbers AL122127 (being 5') and Z17370 (being 3'). The 3' nucleotides (up to about 15 nucleotides) of Ig gamma-1 RPA probes which are in addition to the Ig gamma-1 probe sequence depicted in Figure 3 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of AL122127 and Z17370 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 20, line 28, with the following rewritten paragraph:

— RPA probes include for example the germline Ig gamma-2 probe depicted in Figure 3, sheet 2 (SEQ ID NO:4). This RPA probe comprises a nucleic acid sequence about 632 nucleotides in length. In a preferred embodiment, the present invention provides Ig gamma-2 RPA probes consisting essentially of nucleotides from about 1 to about 630 of the Ig gamma-2 probe depicted in Figure 3. In another preferred embodiment, the present invention provides Ig gamma-2 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 630 or about 620 or about 610 or about 600 or about 590 or about 580 or about 570 or about 560 or about 550 or about 540 or about 530 or about 520 or about 510 or about 500 or about 490 or about 480 or about 470 or about 460 or about 450 or about 440 or about 430 or about 420 or about 410 or about 400 or about 390 or about 380 of the Ig gamma-2 probe depicted in Figure 3.—

Please replace the paragraph beginning at page 21, line 3, with the following rewritten paragraph:

— Also provided by the present invention is the germline Ig gamma-2 probe depicted in Figure 4, sheet 2 (SEQ ID NO:11). This RPA probe comprises a nucleic acid sequence about 387 nucleotides in length. The Ig gamma-2 probe sequence depicted in Figure 4 is preferred over the Ig gamma-2 probe sequence depicted in Figure 3 (SEQ ID NO:4). In a preferred embodiment, the present invention provides Ig gamma-2 RPA probes consisting essentially of nucleotides from about 1 to about 385 of the Ig gamma-2 probe depicted in Figure 4. In another preferred embodiment, the present invention provides Ig gamma-2 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10 to about 385 or about 380 or about 375 or about 370 of the Ig gamma-2 probe depicted in Figure 4.—

Please replace the paragraph beginning at page 21, line 11, with the following rewritten paragraph:

— Also provided herein are Ig gamma-2 RPA probes comprising nucleic acid sequences longer than that depicted in Figure 3 (SEQ ID NO:4), which comprise the Ig gamma-2 nucleic acid sequence depicted in Figure 3 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig gamma-2 probes are designed as complements of fragments of the nucleic acid sequence conceptually generated by fusion of the nucleic acid sequences depicted at Genbank

accession numbers U39934 (being 5') and J00230 (being 3'). The 3' nucleotides (up to about 15 nucleotides) of Ig gamma-2 RPA probes which are in addition to the Ig gamma-2 probe sequence depicted in Figure 3 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of U39934 and J00230 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 21, line 20, with the following rewritten paragraph:

— RPA probes include for example the germline Ig gamma-3 probe depicted in Figure 3, sheet 2 (SEQ ID NO:5). This RPA probe comprises a nucleic acid sequence about 650 nucleotides in length. In a preferred embodiment, the present invention provides Ig gamma-3 RPA probes consisting essentially of nucleotides from about 1 to about 650 of the Ig gamma-3 probe depicted in Figure 3. In another preferred embodiment, the present invention provides Ig gamma-3 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 650 or about 640 or about 630 or about 620 or about 610 or about 600 or about 590 or about 580 or about 570 or about 560 or about 550 or about 540 or about 530 or about 520 or about 510 or about 500 or about 490 or about 480 or about 470 or about 460 or about 450 or about 440 or about 430 or about 420 or about 410 or about 400 or about 390 of the Ig gamma-3 probe depicted in Figure 3.—

Please replace the paragraph beginning at page 21, line 30, with the following rewritten paragraph:

— Also provided by the present invention is the germline Ig gamma-3 probe depicted in Figure 4, sheet 2 (SEQ ID NO:12). This RPA probe comprises a nucleic acid sequence about 391 nucleotides in length. The Ig gamma-3 probe sequence depicted in Figure 4 is preferred over the Ig gamma-3 probe sequence depicted in Figure 3 (SEQ ID NO:5). In a preferred embodiment, the present invention provides Ig gamma-3 RPA probes consisting essentially of nucleotides from about 1 to about 390 of the Ig gamma-3 probe depicted in Figure 4. In another preferred embodiment, the present invention provides Ig gamma-3 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 390 or about 385 or about 380 or about 375 of the Ig gamma-3 probe depicted in Figure 4.—

Please replace the paragraph beginning at page 22, line 4, with the following rewritten paragraph:

— Also provided herein are Ig gamma-3 RPA probes comprising nucleic acid sequences longer than that depicted in Figure 3 (SEQ ID NO:5), which comprise the Ig gamma-3 nucleic acid sequence depicted in Figure 3 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig gamma-3 probes are designed as complements of fragments of the nucleic acid sequence conceptually generated by fusion of the nucleic acid sequences depicted at Genbank accession numbers AL122127 (being 5') and X16110 (being 3'). The 3' nucleotides (up to about

15 nucleotides) of Ig gamma-3 RPA probes which are in addition to the Ig gamma-3 probe sequence depicted in Figure 3 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of AL122127 and X16110 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 22, line 13, with the following rewritten paragraph:

— RPA probes include for example the germline Ig gamma-4 probe depicted in Figure 3, sheet 3 (SEQ ID NO:6). This RPA probe comprises a nucleic acid sequence about 706 nucleotides in length. In a preferred embodiment, the present invention provides Ig gamma-4 RPA probes consisting essentially of nucleotides from about 1 to about 705 of the Ig gamma-4 probe depicted in Figure 3. In another preferred embodiment, the present invention provides Ig gamma-4 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 705 or about 695 or about 685 or about 675 or about 665 or about 655 or about 645 or about 635 or about 625 or about 615 or about 605 or about 595 or about 585 or about 575 or about 565 or about 555 or about 545 or about 535 or about 525 or about 515 or about 505 or about 495 of the Ig gamma-4 probe depicted in Figure 3.—

Please replace the paragraph beginning at page 22, line 22, with the following rewritten paragraph:

— Also provided by the present invention is the germline Ig gamma-4 probe depicted in Figure 4, sheet 3 (SEQ ID NO:13). This RPA probe comprises a nucleic acid sequence about 497 nucleotides in length. The Ig gamma-4 probe sequence depicted in Figure 4 is preferred over the Ig gamma-4 probe sequence depicted in Figure 3 (SEQ ID NO:6). In a preferred embodiment, the present invention provides Ig gamma-4 RPA probes consisting essentially of nucleotides from about 1 to about 495 of the Ig gamma-4 probe depicted in Figure 4. In another preferred embodiment, the present invention provides Ig gamma-4 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 495 or about 490 or about 485 or about 480 of the Ig gamma-4 probe depicted in Figure 4.—

Please replace the paragraph beginning at page 22, line 30, with the following rewritten paragraph:

— Also provided herein are Ig gamma-4 RPA probes comprising nucleic acid sequences longer than that depicted in Figure 3 (SEQ ID NO:6), which comprise the Ig gamma-4 nucleic acid sequence depicted in Figure 3 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig gamma-4 probes are designed as complements of fragments of the nucleic acid sequence conceptually generated by fusion of the nucleic acid sequences depicted at Genbank accession numbers X56796 (being 5') and K01316 (being 3'). The 3' nucleotides (up to about 15

nucleotides) of Ig gamma-4 RPA probes which are in addition to the Ig gamma-4 probe sequence depicted in Figure 3 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of X56796 and K01316 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 23, line 5, with the following rewritten paragraph:

— RPA probes include for example the germline Ig α -1 probe depicted in Figure 4, sheet 1 (SEQ ID NO:7). This RPA probe comprises a nucleic acid sequence about 400 nucleotides in length. In a preferred embodiment, the present invention provides Ig α -1 RPA probes consisting essentially of nucleotides from about 1 to about 400 of the Ig α -1 probe depicted in Figure 4. In another preferred embodiment, the present invention provides Ig α -1 RPA probes consisting essentially of nucleotides from about 1 or about 5 or about 10, to about 400 or about 395 or about 390 or about 385 of the Ig α -1 probe depicted in Figure 4.

Please replace the paragraph beginning at page 23, line 12, with the following rewritten paragraph:

— Also provided herein are Ig α -1 RPA probes comprising nucleic acid sequences longer than that depicted in Figure 4 (SEQ ID NO:7), which comprise the Ig α -1 nucleic acid sequence depicted in Figure 4 and additionally comprise about 5, or about 10, or about 15 additional nucleotides at the 3' terminus. Ig α -1 probes are designed as complements of fragments of the nucleic acid sequence conceptually generated by fusion of the nucleic acid sequences depicted at Genbank accession numbers L04541 (being 5') and BC005951 (being 3'). The 3' nucleotides (up to about 15 nucleotides) of Ig α -1 RPA probes which are in addition to the Ig α -1 probe sequence depicted in Figure 4 comprise a nucleic acid sequence which is additionally complementary to the fused sequence of L04541 and BC005951 and contiguous with the preceding complementary sequence.—

Please replace the paragraph beginning at page 23, line 28, with the following rewritten paragraph:

— Preferred probe sequences of the invention are shown in the figures. Figure 3 (SEQ ID NOS:1-6) depicts some “longer” probes and Figure 4 (SEQ ID NOS:7-13) some shorter, preferred versions. Thus, preferred probes include nucleic acids consisting essentially of the sequences shown in Figure 3 or 4.—

On page 28, immediately preceding the heading “CLAIMS”, please insert the enclosed text entitled “SEQUENCE LISTING” into the specification.